

REMARKS

No amendments to the application or claims have been made in this Reply.

Claims 18-81 are pending in the application, with claims 18, 34, 39, 58 and 66 being the independent claims. Claims 34 and 38 have been withdrawn from consideration by the Examiner.

Applicants respectfully traverse all of the rejections in the Office Action.

I. The Rejection of Claims 18-19, 21-27, 39-40 and 42-48 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 18-19, 21-27, 39-40 and 42-48 have been rejected at pages 2-5 of the Office Action as allegedly being unpatentable over Zimmermann, U.S. Patent No. 6,465,226 (hereinafter "Zimmermann") in view of Kyekyoon *et al.*, Published International Patent Application No. WO 02/13789 (hereinafter "Kyekyoon"). Applicants respectfully traverse this rejection.

The Office Action suggests that Zimmermann discloses a process for preparing microspheres comprising an ionically crosslinked polymer, the process comprising producing liquid droplets from a solution comprising an ionically crosslinkable polymer into a gas stream using a nozzle, dropping the droplets carried by the gas stream into a gelling solution, whereby crosslinked polymer microspheres are formed, and separating the microspheres from the gelling solution by centrifugation.

The Office Action concedes that "Zimmermann does not teach forming a continuous gas stream by using an ultrasonic nebulizer and transferring the gas stream into the gelling solution." Office Action at page 3, fourth paragraph. The Office Action attempts to cure this deficiency with the disclosure of Kyekyoon, asserting that this reference discloses forming particles by using an ultrasonic nebulizer to nebulize a liquid into a continuous gas stream, and transferring the gas stream into a gelling solution. The Office Action concludes that it would have been obvious to modify Zimmermann's process with Kyekyoon, since Kyekyoon offers a solution for a microencapsulation process that produces microparticles of controlled sizes. Applicants respectfully disagree with these contentions and conclusions.

Applicants submit that each of the processes set forth in present independent claims 18, 39, 59 and 66, recite the formation of a “continuous gas stream by using an ultrasonic nebulizer.” As conceded in the Office Action, Zimmerman fails to disclose this element of the present claims. *See* Office Action at page 3, fourth paragraph. Applicants respectfully submit, contrary to the assertions in the Office Action, that Kyekyoon also fails to disclose this element, and thus fails to cure the deficiencies in Zimmerman.

The methods disclosed in Kyekyoon do not form a continuous gas stream by using an ultrasonic nebulizer. Instead, the methods of Kyekyoon are directed to the formation of a *stream of liquid, not a stream of gas*, that is broken into droplets by an acoustic-type wave. As discussed in Kyekyoon:

The instant invention relates to a process for making micro- and nano-sized spherical particles comprising pumping a material through a small orifice and then *shaking said liquid* with an acoustic type-wave to produce micro- and nano-sized spherical particles.

Kyekyoon at page 12, first paragraph (emphasis added). “The *stream of liquid* exiting the orifice is broken into droplets by vibrating or shaking the device at a controlled frequency and amplitude.” *Id.* at page 14, second full paragraph (emphasis added).

Kyekyoon further states:

Not to be bound by theory, the reason for this reduction in drop size is believed to be that there are two forces present, gravitational and electrical, that are working together to *pull the liquid off of the nozzle*, while surface tension forces hold the liquid at the nozzle.

Id. at page 15, first paragraph (emphasis added).

The Office Action asserts that the passage at page 19, lines 10-13, and Figures 7 and 8, of Kyekyoon, disclose formation of a continuous gas stream using an ultrasonic nebulizer. Applicants respectfully disagree with these assertions.

The passage appearing at page 19, lines 5-13 of Kyekyoon is reproduced below (emphasis added):

Illustratively, particle or sphere formation is accomplished by *pumping a liquid* material (e.g., polymer dissolved in organic solvent, polymer melts, etc.) through a small orifice (several millimeters to 10 micrometers in diameter). The *stream of liquid* exiting the orifice is broken by vibrating or shaking the device at a controlled frequency and amplitude.

The vibration or shaking can be achieved by, for example, a piezoelectric transducer driven by a wave generator. It is believed that the mechanical excitation launches a wave of acoustic energy along the liquid jet generating periodic instabilities that, in turn, *break the stream* into a train of droplets.

Applicants submit that the “stream” referred to at line 13, is the “stream of liquid” that exits the orifice of the nozzle. Thus, Kyekyoon does not generate a “continuous gas stream” as recited in the presently claimed invention. Instead, a liquid stream is generated.

In addition, Applicants submit that the “wave of acoustic energy” referred to in Kyekyoon is not the same as an ultrasonic nebulizer, which via ultrasonic influence, produces an aerosol fog above a liquid surface. As discussed in Kyekyoon, the acoustic energy merely acts to *pull the droplets* from the nozzle, there is no aerosol formation. See Kyekyoon at page 15, first paragraph. Kyekyoon relies on pumping a liquid through a small orifice, which is then pulled from the nozzle.

The distinction from Kyekyoon is further illustrated at the paragraph bridging pages 26-27, that describe the elements of Figure 7 (emphasis added):

An embodiment of an apparatus of the present invention is illustrated in Figure 7. The apparatus 10 includes a nozzle 12 through which *the solution 20 passes, forming a jet 14*. A carrier stream 18 of a *non-solvent liquid* flows around the jet, increasing the velocity of the jet. Vibrations are induced to breakup the jet into particles, in this case using a piezoelectric transducer 16 driven by a frequency generator 24 through an amplifier 22.

Applicants submit that Figure 7 describes an apparatus in which a first liquid is passed through a nozzle forming the droplets, is transferred to second liquid, which acts as a carrier. This second liquid acts to “pull the liquid off of the nozzle.” See Kyekyoon at page 15, lines 7-8. Thus, Kyekyoon describes a process in which an additional mechanical force is required, in order to effect the nozzle-based droplet generation of the first liquid, i.e., the pumping force and/or the pulling force of the second liquid. This principle is in stark contrast to the basic principle of an acoustic nebulizer, in which droplets form without any additional pushing or pulling force above a surface of the liquid.

Applicants submit that Kyekyoon, in addition to not disclosing an acoustic nebulizer, in fact teaches away from such a device, as a person of ordinary skill in the art would not be

inclined to replace the *essential* pumping/pulling process disclosed in Kyekyoon, with an acoustic nebulizer. See Kyekoon at page 11, first paragraph (emphasis added), “[t]his technique is novel and very useful in that it is particularly suited to fabricating micrometer- and nanometer-size hollow and multi-shell spheres *which would be essentially impossible to create with any other existing techniques.*”

Applicants submit that Kyekyoon does not disclose the formation of a continuous gas stream, in any form, as the methods and apparatus disclosed throughout Kyekyoon all refer to the formation of a *stream of liquid* containing the formed droplets. In addition, Kyekyoon does not disclose the use of an acoustic nebulizer, and in fact teaches away from the use of such a device.

Applicants therefore submit that Kyekyoon does not cure the deficiencies present in Zimmermann. Thus, the Office Action has not set forth a *prima facie* case of obviousness. See M.P.E.P. § 2141.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

II. The Rejection of Claims 20, 28, 41 and 49 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 20, 28, 41 and 49 have been rejected at pages 5-6 of the Office Action as allegedly being unpatentable over Zimmermann in view of Kyekyoon and further in view of Lim, U.S. Patent No. 4,352,883 (hereinafter “Lim”). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann and Kyekyoon disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the polyvalent cation of the gelling solution is selected from the compositions set forth in present claims 20 or 41, or that the metal cation is Ca^{2+} , as set forth in present claims 28 or 49. The Office Action attempts to cure these deficiencies with the disclosure of Lim, suggesting that Lim discloses the polyvalent cation polyethyleneimine of a gelling solution and the use of Ca^{2+} as the metal cation of a gelling solution. The Office Action

therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Kyekyoon does not support a *prima facie* case of obviousness. Lim fails to cure these deficiencies as it provides no disclosure of the formation of a continuous gas stream using an ultrasonic nebulizer. Thus, Zimmermann, Kyekyoon and Lim, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

III. The Rejection of Claims 29-30, 32, 35-37, 50-51, 53 and 55-57 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 29-30, 32, 35-37, 50-51, 53 and 55-57 have been rejected at pages 6-9 of the Office Action as allegedly being unpatentable over Zimmermann in view of Kyekyoon and further in view of Andersson *et al.*, Published International Patent Application No. WO 03/091315 (hereinafter "Andersson"). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann and Kyekyoon disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the gelling solution additionally comprises surfactant present in an amount of from 0.05% to .15% by weight; that the solution of the ionically crosslinkable polyionic polymer is kept within a temperature range of 25 to 35°C; or filtering the microspheres through a screen. The Office Action attempts to cure these deficiencies with the disclosure of Andersson, indicating that Andersson discloses the addition of surfactant to a gelling solution, and the use of a temperature of 40°C, and filtering beads through a sieve. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Kyekyoon does not support a *prima facie* case of obviousness. Andersson fails to cure these deficiencies as it provides no disclosure of the formation of a continuous gas stream using an

ultrasonic nebulizer. Thus, Zimmermann, Kyekyoon and Andersson, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

IV. The Rejection of Claims 31, 52 and 79 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 31, 52 and 79 have been rejected at pages 9-10 of the Office Action as allegedly being unpatentable over Zimmermann in view of Kyekyoon and Andersson and further in view of Lemoine *et al.*, *International Journal of Pharmaceutics* 176:9-19 (1998) (hereinafter "Lemoine"). Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Kyekyoon and Andersson disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the surfactant is selected from those compositions set forth in present claims. The Office Action attempts to cure these deficiencies with the disclosure of Lemoine, indicating that Lemoine discloses the use of polyoxyethylene sorbitan trioleate as a surfactant in the production of alginate microspheres. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Kyekyoon and Andersson does not support a *prima facie* case of obviousness. Lemoine fails to cure these deficiencies as it provides no disclosure of the formation of a continuous gas stream using an ultrasonic nebulizer. Thus, Zimmermann, Kyekyoon, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

V. The Rejection of Claims 33 and 54 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 33 and 54 have been rejected at pages 10-12 of the Office Action as allegedly being unpatentable over Zimmermann in view of Kyekyoon and further in view of Vasington *et*

al., U.S. Patent No. 5,387,522 (hereinafter "Vasington"), Andersson and Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Kyekyoon, Andersson and Lemoine disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the solution comprises 0.75% to 1.5% by weight of sodium alginate. The Office Action attempts to cure these deficiencies with the disclosure of Vasington, indicating that Vasington discloses the use of low viscosity sodium alginates at about 0.5% to about 1.4%. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann and Kyekyoon does not support a *prima facie* case of obviousness. Vasington, Andersson and Lemoine fail to cure these deficiencies as they provide no disclosure of the formation of a continuous gas stream using an ultrasonic nebulizer. Thus, Zimmermann, Kyekyoon, Vasington, Andersson and Lemoine, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

VI. The Rejection of Claims 58-64 and 65 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 58-64 and 65 have been rejected at pages 12-16 of the Office Action as allegedly being unpatentable over Zimmermann in view of Kyekyoon, Lim, Andersson and Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Kyekyoon, Lim, Andersson and Lemoine disclose the claimed invention, including the use of the specifically claimed amount of sodium alginate and the specified gelling solution. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Kyekyoon, Lim, Andersson and Lemoine does not support a *prima facie* case of obviousness, as none of

these references, alone or in combination, disclosure of the formation of a continuous gas stream using an ultrasonic nebulizer.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

VII. The Rejection of Claims 66-67, 69-75, 77-78 and 81 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 66-67, 69-75, 77-78 and 81 have been rejected at pages 16-19 of the Office Action as allegedly being unpatentable over Zimmermann in view of Kyekyoon and Andersson. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Kyekyoon, and Andersson disclose the claimed invention, including the use of the specifically claimed temperature range. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Kyekyoon and Andersson does not support a *prima facie* case of obviousness, as none of these references, alone or in combination, disclosure of the formation of a continuous gas stream using an ultrasonic nebulizer.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

VIII. The Rejection of Claims 68 and 76 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 68 and 76 have been rejected at pages 19-20 of the Office Action as allegedly being unpatentable over Zimmermann in view of Andersson and Kyekyoon and further in view of Lim. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Andersson and Kyekyoon disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the polyvalent cation of the gelling solution is selected from the compositions set forth in the present claims, or that the metal cation is Ca²⁺. The Office Action attempts to cure these deficiencies with the disclosure of Lim, suggesting that

Lim discloses the polyvalent cation polyethyleneimine of a gelling solution and the use of Ca²⁺ as the metal cation of a gelling solution. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Andersson and Kyekyoon does not support a *prima facie* case of obviousness. Lim fails to cure these deficiencies as it provides no disclosure of the formation of a continuous gas stream using an ultrasonic nebulizer. Thus, Zimmermann, Andersson, Kyekyoon and Lim, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

IX. The Rejection of Claim 80 Under 35 U.S.C. § 103(a) Should be Withdrawn

Claim 80 has been rejected at pages 20-22 of the Office Action as allegedly being unpatentable over Zimmermann in view of Kyekyoon and Andersson further in view of Vasington and Lemoine. Applicants respectfully traverse this rejection.

The Office Action suggests that the combined disclosures of Zimmermann, Kyekyoon, and Andersson disclose the claimed invention as set forth above. The Office Action, however, indicates that these references do not disclose that the solution comprises the specifically claimed components. The Office Action attempts to cure these deficiencies with the disclosure of Vasington, indicating that Vasington discloses the use of low viscosity sodium alginates at about 0.5% to about 1.4%. The Office Action therefore concludes that the claimed invention would have been obvious. Applicants respectfully disagree with these contentions and conclusions.

As set forth above, Applicants submit that the combination of Zimmermann, Kyekyoon, Andersson, Vasington and Lemoine fail to disclose the formation of a continuous gas stream using an ultrasonic nebulizer. Thus, the cited references, alone or in combination, do not disclose the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

X. Conclusion

Applicants believe that the claims of the present application are in condition for allowance and respectfully request allowance thereof. The Examiner is invited to telephone the undersigned if that would be helpful in resolving any issues.

With the exception of extension of time fees, no fees are believed due for this submission. The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application or credit any overpayment, to Deposit Account No. 50-5071. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-5071.

Respectfully submitted,

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